THE YEAR IN HYPERTENSION

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Preface

HARALAMBOS GAVRAS

Cardiovascular disease is firmly established as the number one cause of morbidity and mortality throughout the world. Having remained at the top of the list in Western countries in the last decades of the 20th century, it is now rapidly rising in incidence and prevalence in the developing world. Admittedly, this is the consequence of successful implementation of medical, social, and economic policies in much of the world, which have led to limitation or eradication of infectious diseases, decline in deaths from cancer, diminished violence from international conflicts, increased supply of food, and prolonged life expectancy. Also, successful treatment of acute disorders has resulted in medical conditions that require chronic management. Accompanying these demographic factors has been an explosive development in medical technology with diagnostic and therapeutic applications.

The ever-expanding field of cardiovascular research has led to a huge number of publications in specialized medical journals. For the practising physicians and other medical specialists it is a daunting task to try to keep up with this onslaught and, in particular, to sort out from this wealth of information the pieces that are clinically meaningful and may impact their practices. Since hypertension is central in the causality, severity, and progression of many cardiovascular disorders, any progress in its prevention, diagnosis, or treatment has ramifications affecting many related disorders. We therefore asked a number of distinguished hypertension specialists to evaluate the latest literature in their particular areas of expertise and choose the most important and clinically significant advances that would be of interest to a wide range of busy clinicians. The results of this effort are the following eleven chapters that cover the latest 'hot topics' in clinical research of hypertension. Each chapter offers a summary of some of the most important papers in that topic, and their authors' interpretation of the results, as well as the contributing specialists' commentary on the validity of the findings, their scientific strengths and possible caveats, their clinical applicability and their overall potential impact on healthcare.

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4. Krushkal J, Ferrell R, Mockrin SC, Turner ST, Sing CF, Boerwinkle E. Genome-wide linkage analyses of systolic blood pressure using highly discordant siblings. *Circulation* 1999; 99: 1407–10.
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The epidemiology of hypertension

JAN A STAESSEN, TATIANA KUZNETSOVA, JIGUANG WANG

Introduction

The very foundation of scientific progress lies in careful observation of the natural world. Epidemiology is centred on the observation and the mathematical modelling of phenomena, which describe the continuum between health and disease, and which occur cross-sectionally or prospectively within or across populations. Although individuals are usually the unit of observation in epidemiological studies, the use of populations or large samples distinguishes epidemiology from clinical medicine.

In general, epidemiological research focuses on the health status of populations, the explanation of the aetiology of diseases by determining the factors that may cause specific disorders, the prediction of disease occurrences, and the prevention of new occurrences, or the improvement of the health status of those already afflicted. Implied in these activities are two different research goals: (i) a better understanding of pathogenetic processes, and (ii) prevention of disease. Our update of the literature reflects this dichotomy of epidemiology, being on the one hand explanatory or fundamental, versus pragmatic and action-oriented on the other.

A systematic review of the relevant literature published in 2003 was beyond the scope of this chapter. However, to illustrate progress along the two avenues of research outlined above, we have summarized contributions to the field of genetic epidemiology (mechanisms of disease) and reviewed recent publications focusing on the relation between cardiovascular complications, in particular stroke, and blood pressure (BP) (prevention of disease).

Mechanisms of disease

Until now, geneticists have failed to identify common genes having a large impact on human hypertension and the associated complications. We believe that such genes do not exist, and that in populations the distribution of complex cardiovascular traits, such as BP or left ventricular mass, depend on a mosaic of many interacting genetic loci, each with a small influence on the phenotype or with a contribution

differing according to gender [1], race [2,3], age [2,4], or lifestyle [4]. Four recently published papers illustrate gender-specific mechanisms in the inheritance of left ventricular mass, the importance of novel pathogenetic mechanisms in the causation of hypertension, and the influence of lifestyle factors, such as sodium intake or alcohol consumption on the genetic determination of continuous phenotypes.

Maternal and paternal influences on left ventricular mass of offspring

Kuznetsova T, Staessen JA, Olszanecka A, *et al.*, on behalf of the European Project On Genes in Hypertension (EPOGH) Investigators. *Hypertension* 2003; **41**(1): 69–74

BACKGROUND. Among first-degree relatives, there is significant concordance in left ventricular mass, but the specific gender-specific parental influences on left ventricular mass of offspring were not known. Kuznetsova *et al.* evaluated familial aggregation of left ventricular mass by type of familial relation in a random sample of 159 nuclear families (250 parents and 321 offspring) recruited from two European populations of Caucasian extraction. Mean age of parents and offspring was 51.4 years and 25.1 years, respectively. The authors performed two-dimensionally guided M-mode echocardiography to determine left ventricular mass. They computed correlation coefficients for left ventricular mass as measure of concordance (positive correlation) or discordance (non-significant correlation) between first-degree relatives and between spouse pairs.

INTERPRETATION. After adjustment for country, gender, age, height, body weight, systolic blood pressure (SBP), antihypertensive treatment, smoking, alcohol intake, and physical activity, the intrafamilial correlations for left ventricular mass were 0.06 ($P = 0.57$) in 91 spouse–spouse pairs, 0.14 ($P = 0.002$) in 500 parent–offspring pairs, and 0.32 ($P < 0.001$) in 179 sib–sib pairs. Across the 4 parent–offspring relations, the mother–son ($n = 140$; $r = 0.27$; $P < 0.001$) and mother–daughter ($n = 161$; $r = 0.28$; $P < 0.001$) correlations were significant, whereas the father–son ($n = 101$; $r = 0.04$; $P = 0.69$) and father–daughter ($n = 98$; $r = -0.09$ $P = 0.38$) correlations were not different from nought (Fig. 8.1). Overall, the mother–offspring correlation coefficient was significantly higher than the father–offspring correlation ($r = 0.28$ vs $r = -0.04$; $P = 0.005$). These findings therefore suggest that maternal factors affect left ventricular mass of offspring more than paternal influences.

Comment

Left ventricular structure is a complex multigenic trait influenced by variation in many genes. Because most of these polymorphisms have not yet been identified or studied, it is currently impossible to estimate their collective contribution to left ventricular mass. However, classic heritability studies, such as reported here provide insight as to what extent genetic factors impact on a trait. Left ventricular mass was significantly concordant among siblings and mother–offspring pairs, but not in father–offspring pairs or between spouses. Kuznetsova *et al.* excluded false paternity,

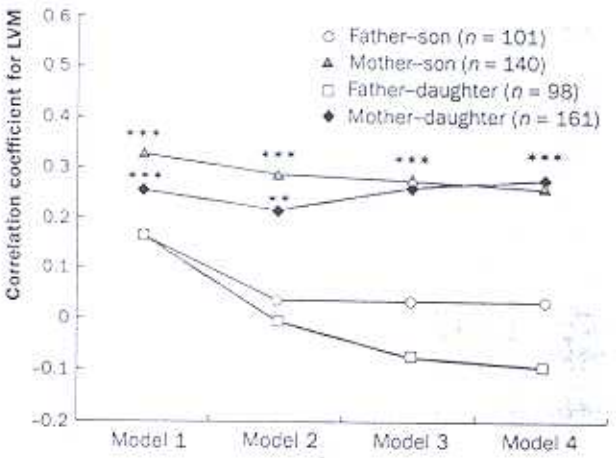

Fig. 8.1 Gender-specific intrafamilial correlations for left ventricular mass. Model 1 is adjusted for country, sex and age. The three other models reflect further cumulative adjustments for height and body weight (Model 2), for systolic blood pressure and antihypertensive treatment (Model 3), and in addition for lifestyle factors including smoking, alcohol intake and physical activity (Model 4). LVM, left ventricular mass. $^{**}P < 0.01$; $^{***}P < 0.001$: significance of the intraclass correlation coefficients. Source: Kuznetsova *et al.* (2003).

consanguinity among families and type I error as possible explanations for the divergent parent–offspring correlations. Without stratification for gender, the intrafamilial correlations for left ventricular mass and body weight and height given in this paper were similar to those published by other investigators [5–7] and supported the validity of the findings. Further studies are required to elucidate the genetic, epigenetic and ecogenetic mechanisms underlying the strong maternal influence on left ventricular mass. Possible mechanisms include transmission of the mitochondrial DNA from mother to offspring, different expression of the parental alleles as a consequence of genomic imprinting, and/or the influence of the intrauterine environment on fetal development.

Salt, endogenous ouabain and blood pressure interactions in the general population

Wang JG, Staessen JA, Messaggio E, *et al. J Hypertens* 2003; **21**(8): 1475–81

BACKGROUND. Ouabain is an inhibitor of the sodium–potassium pump, which plays an important role in sodium homeostasis and BP regulation [8,9]. Wang *et al.*

investigated the plasma concentration of endogenous ouabain in a Belgian population sample (n = 379) in relation to BP, the Gly460Trp polymorphism of the α-adducin gene, and other determinants of sodium homeostasis.

INTERPRETATION. Plasma ouabain (median 140 pmol/L) correlated independently and positively with male gender (n = 182; P = 0.002), smoking (n = 116; P = 0.05), urinary potassium excretion (mean 69 mmol/day; P <0.0001), and the Trp mutation in the α-adducin gene (n = 161; P <0.0001). Both before and after adjustment for covariables, continuous as well as categorical analyses revealed a significant interaction (P ≤0.02) between plasma ouabain and urinary sodium excretion (mean 194 mmol/day) in relation

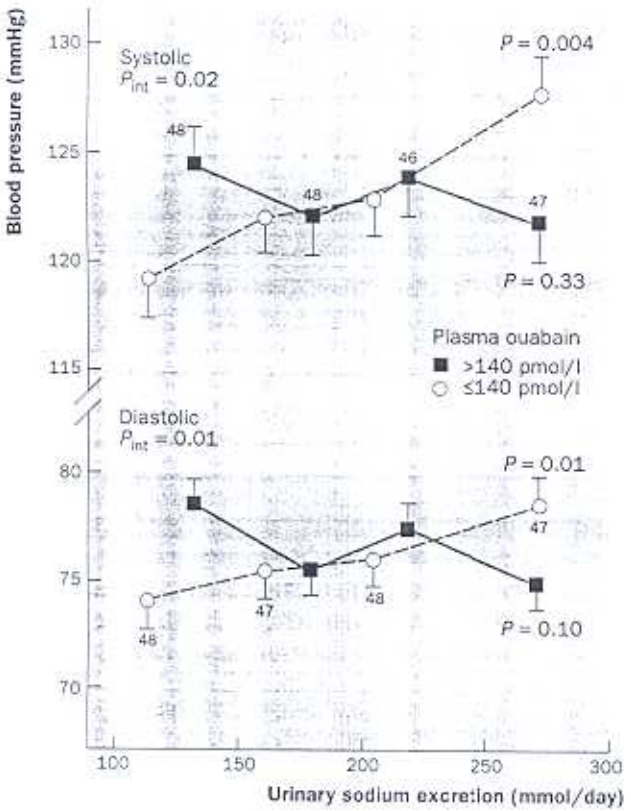

Fig. 8.2 Associations between BP, plasma ouabain concentration and urinary sodium excretion. Filled symbols (plasma ouabain >140 pmol/l [median]) and open symbols (≤140 pmol/l) represent the mean values of BP in quartiles of urinary sodium excretion. The number of individuals in each quartile of urinary sodium excretion is shown alongside the symbols. Vertical lines denote SEs. Values were adjusted for gender, age, age^2, body mass index, smoking, alcohol intake, and use of antihypertensive drugs and/or oral contraceptives. Significance levels for trends (P) and interactions (P_{int}) are given. Source: Wang *et al.* (2003).

to BP (mean systolic/diastolic pressure: 123/76 mmHg). In individuals with plasma ouabain values below the median, BP increased (P ≤0.01) by 2.2 mmHg systolic and 1.4 mmHg diastolic for each 50 mmol/day increment in urinary sodium excretion (Fig. 8.2). No association between BP and urinary sodium excretion was found when plasma ouabain exceeded the median. Thus, plasma ouabain behaved as a BP modulating factor, possibly released in response to potassium, either inhibiting the pressor effect of an excessive salt intake or counteracting the depressor action of sodium depletion.

Comment

The hormone ouabain is released endogenously from the adrenal glands and possibly from the midbrain [10]. Depending on its concentration, endogenous ouabain behaves as a versatile modulator of the ubiquitously expressed sodium pump [11]. Recent experiments provide some insight into the mechanisms possibly explaining Wang *et al.*'s epidemiological findings. In renal tubular cells, inhibition of Na^+, K^+–ATPase activity by ouabain promotes natriuresis. In contrast, at very low concentrations within the nanomolar range, endogenous ouabain may increase the size of the membrane pool of active sodium pumps [12] and via this or other unknown mechanisms lead to renal sodium conservation rather than salt loss [11].

Relationship between left ventricular mass and the ACE *D/I* polymorphism varies according to sodium intake

Kuznetsova T, Staessen JA, Stolarz K, *et al.*, on behalf of the European Project On Genes in Hypertension (EPOGH) Investigators. *J Hypertension* 2004; **22**(2): 287–95.

BACKGROUND. The renin–angiotensin–aldosterone system (RAAS) regulates myocardial growth system-wide and at the tissue level. Key enzymes in the RAAS cascade are the angiotensin converting enzyme (ACE) and aldosterone synthase (CYP11B2). In the European Project on Genes in Hypertension (EPOGH), Kuznetsova *et al.* investigated to what extent left ventricular mass in populations and families relates to the angiotensin converting enzyme (ACE *D/I*) and aldosterone synthase (CYP11B2 *–344C/T*) polymorphisms and urinary sodium excretion. The EPOGH researchers randomly recruited 219 nuclear families (382 parents and 436 offspring) in Cracow (Poland), Novosibirsk (Russia), and Mirano (Italy). For statistical analysis, they implemented a population based and family based approach and used generalized estimating equations and the quantitative transmission disequilibrium test, respectively.

INTERPRETATION. The EPOGH investigators found significant differences between the two Slavic centres and Mirano in left ventricular mass index (LVMI) (94.9 vs 80.3 g/m^2), sodium excretion (229 vs 186 mmol/day), and the prevalence of the ACE *D* allele (52.1 vs 58.5%). There was significant heterogeneity between Slavic nationals and Italians in the phenotype–genotype relations for ACE, but not for CYP11B2. In the two Slavic centres, ACE *II* homozygosity was significantly associated with higher LVMI in populations

based as well as in family based analyses. By contrast, in Mirano, LVMI was slightly higher in *DD* homozygotes ($P = 0.05$), but only in the population based approach. LVMI increased with higher sodium excretion in ACE *II* homozygous offspring of both Slavic and Italian extraction (+4.2 ± 2.1 g/m²/100 mmol; $P = 0.04$) and in Slavic (+2.6 ± 1.1 g/m²/100 mmol; $P = 0.02$), but not Italian (−3.3 ± 3.2 g/m²/100 mmol; $P = 0.29$) *D* allele carriers (Fig. 8.3). Kuznetsova *et al.* did not find any association between LVMI and the CYP11B2 polymorphism. Thus, the relation between LVMI and the ACE *D/I* polymorphism differs across populations, possibly because of intermediate regulatory mechanisms responsive to varying levels of salt intake.

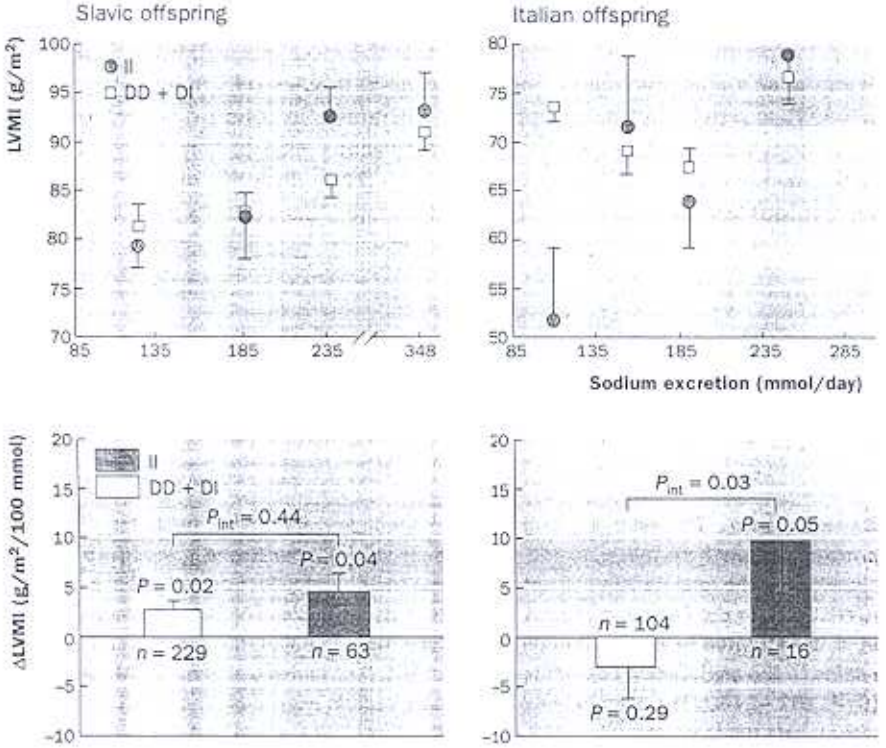

Fig. 8.3 Association between left ventricular mass index (LVMI) and 24-hour urinary sodium excretion by angiotensin converting enzyme (ACE) genotype in 412 untreated offspring of Slavic or Italian origin. LVMI was adjusted for centre (Slavic offspring), sex, age, systolic blood pressure, smoking and alcohol intake. Upper panels show the association in quartiles of the distribution of sodium excretion. Lower panels show differences in LVMI associated in multiple regression analysis with a 100 mmol increase in the 24-hour sodium excretion. P_{int} indicates the *P*-values for interaction between the ACE genotype and 24-hour urinary sodium excretion analysed as a continuous variable. Source: Kuznetsova *et al.* (2004).

Comment

Multiple genes, epistatic interaction among genes, and numerous single nucleotide polymorphisms (SNPs) influence complex traits, such as left ventricular mass. Moreover, as exemplified by our findings, many environmental factors, such as sodium intake, modify the actions of genes. According to current knowledge, systemic ACE activity does not change with salt intake. However, impaired suppression of the RAAS might act as a stimulus increasing left ventricular mass [13]. ACE *II* homozygotes have lower plasma ACE activity than *D* allele carriers. For this reason, one might speculate that the margin of adaptation of RAAS in response to varying levels of sodium intake might be smaller in *II* homozygotes than in *D* allele carriers. In line with this hypothesis, some investigators found that patients homozygous for the *I* allele experienced a significantly greater rise in BP in response to a high salt intake compared to *DD* homozygotes [14,15].

Haematological phenotypes in relation to the *C1797T* β-adducin polymorphism in a Caucasian population

Wang JG, Barlassina C, Bianchi G, Fagard R, Zagato L, Staessen JA. *Clin Sci* 2003; **104**(4): 369–76

Background. The membrane-skeleton protein adducin stimulates the assembly of the spectrin–actin network, which determines the morphology and motility of cells [16]. Adducin is composed of either α and β, or α and γ subunits, which are largely similar in amino acid sequence and domain organization [16]. The α- and γ-adducins are expressed in most tissues, whereas β-adducin is abundant in brain and erythrocytes [16,17]. With the targeted gene knockout approach, two recent studies consistently found that β-adducin deficient mice showed a phenotype of mild compensated haemolytic anaemia characterized by increased osmotic fragility, spherocytosis or elliptocytosis [18,19]. The investigators of the Flemish Study on Environment, Genes and Health Outcomes (FLEMENGHO [20]) investigated whether in humans common haematological phenotypes of red blood cells were associated with the *C1797T* polymorphism in exon 15 of the human β-adducin gene. They studied 802 unrelated individuals and 294 families (459 parents and 609 offspring) randomly selected from a Caucasian population. They employed generalized estimating equations to allow for the non-independence of the observations within families, while controlling for covariables.

Interpretation. In 917 men, with adjustments applied for age, body mass index, serum total cholesterol, smoking, and alcohol intake, *CC* homozygotes had significantly ($P = 0.02$) lower red blood cell count (4.93 vs 4.86 10^{12}/l), haemoglobin (9.30 vs 9.18 mmol/l) and haematocrit (45.0 vs 44.4%) than *T* allele carriers. In 329 men who consumed alcohol (Fig. 8.4), the differences between *CC* homozygotes and *T* allele carriers were 0.13 × 10^{12}/l ($P = 0.02$) for red blood cell count, 0.23 mmol/l ($P = 0.005$) for haemoglobin, and 1.08% ($P = 0.02$) for haematocrit. In 953 women, none of these associations was significant ($P \geq 0.06$), irrespective of alcohol intake (13.3% [$n = 127$]). Thus, in men consuming alcohol, the β-adducin *CC* genotype was associated with lower red blood cell count, haemoglobin, and haematocrit.

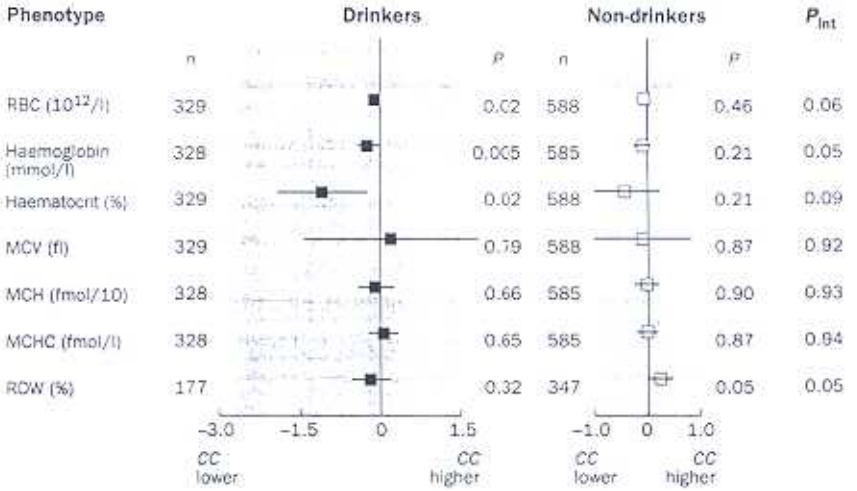

Fig. 8.4 Associations between haematological phenotypes and the β-adducin *C1797T* genetic polymorphism in 917 Belgian men. RBC, rec blood cell; MCV, mean corpuscular volume. MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; RDW, red cell distribution width. The haematological phenotypes were adjusted for age, body mass index, serum total cholesterol and smoking. Closed symbols (drinkers) and open (non-drinkers) symbols represert the mean differences between β-adducin *CC* homozygotes and *T* allele carriers (*CC* minus *T* individuals). Horizontal lines denote 95% confidence intervals. Number of participants (*n*) and significance levels (*P*) for the difference between *CC* homozygotes and *T* allele carriers and for interaction between β-adducin genotype and alcohol intake (P_{int}) are given. Source: Wang *et al.* (2003).

Comment

In epidemiological studies, haematocrit is a major determinant of BP. Wang *et al.* hypothesized that in male β-adducin *CC* homozygotes alcohol consumption exposed the greater fragility of the erythrocyte membrane. This genotype probably potentiated the structural and functional haematological disturbances associated with alcohol intake. In this study, the number of women regularly consuming alcohol was too low to demonstrate this association.

Prevention of disease

To illustrate the action-oriented dimension of epidemiological research, we focused on the close relation between cardiovascular complications and BP and the role of BP lowering in the prevention of stroke.

Hypertension is the most consistent and powerful harbinger of stroke and is involved in nearly 70% of all strokes [21]. Stroke is the second most frequent cause of death worldwide, exceeded only by ischaemic heart disease [22]. In relative terms, stroke incidence is similar in men and women, but race may have a major impact. In the USA, blacks have stroke mortality roughly twice that of whites [21]. In many countries of Western Europe and North America as well as in Japan, age-adjusted stroke rates steadily declined over the past 50 years [23]. Most experts attributed this favourable secular trend to the more accurate primary and secondary prevention, which came with the recognition of the role of cardiovascular risk factors, the availability of powerful and well-tolerated antihypertensive drugs, and the growing prosperity of industrialized countries.

Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data of one million adults in 61 prospective studies

Prospective Studies Collaboration. *Lancet* 2002; **360**(9349): 1903–13

Background. Researchers of the Prospective Studies Collaboration combined information on each of one million adults with no previous cardiovascular disease recorded at baseline in 61 longitudinal studies. During 12.7 million person-years at risk, about 56 000 cardiovascular deaths occurred at ages from 40 to 89 years, including 12 000 deaths from stroke and 34 000 from ischaemic heart disease. The researchers applied a correction for regression dilution bias [24], and calculated the relation between mortality during each decade of age at death and the estimated usual BP at the start of that decade.

Interpretation. Within each decade of age at death, the relative risk associated with a given absolute difference in usual blood pressure was about the same down to at least 115 mmHg systolic (Fig. 8.5) and 75 mmHg diastolic. At ages 40–69 years, each BP difference of 20 mmHg systolic or 10 mmHg diastolic entailed a more than twofold difference in the stroke death rate and twofold differences in the death rates from ischaemic heart disease and other vascular causes. All of these proportional differences in vascular mortality were about half as extreme at ages 80–89 years as at 40–49 years, but the absolute differences in risk were greater at old age. These age-specific associations were similar in men and women.

Comment

The Prospective Studies Collaboration demonstrated that small gradients in systolic or diastolic BP can account for substantial differences in cardiovascular mortality and that the risk starts to increase at levels of BP, which are within the normotensive range.

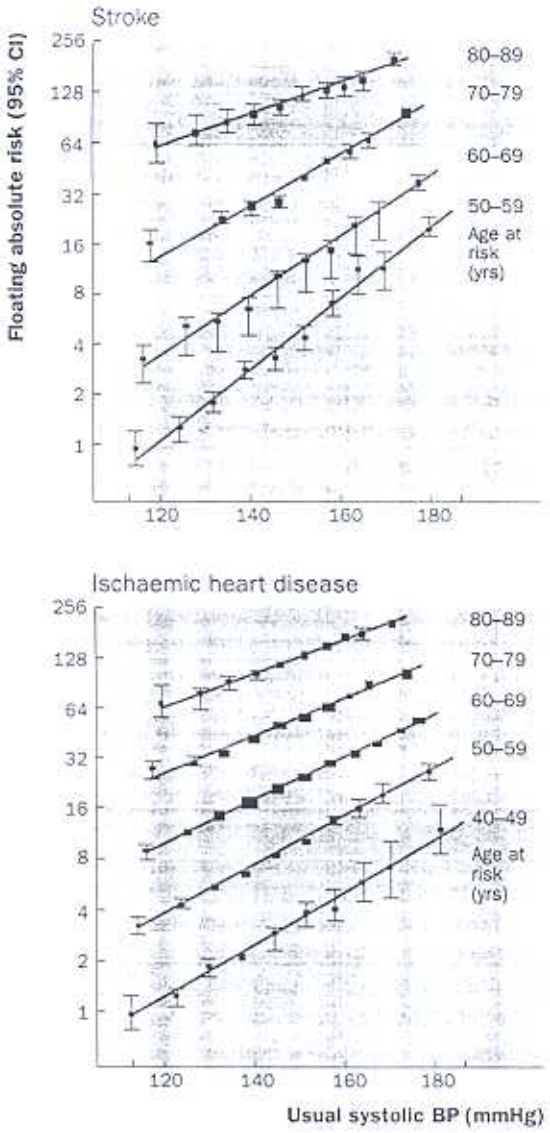

Fig. 8.5 Mortality rates for stroke (top) and ischaemic heart disease (bottom) in decades of age in relation to usual systolic blood pressure at the start of that decade. Rates are plotted on a floating absolute scale and each square has area inversely proportional to the effective variance of the log mortality rate. Source: Prospective Studies Collaboration (2002).

Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States

Wolf-Maier K, Cooper RS, Banegas JR, *et al. JAMA* 2003; **289**(18): 2363–9

Background. BP is the most consistent and powerful predictor of stroke. Nevertheless, the geographical heterogeneity in stroke mortality remains poorly understood. Age-standardized rates vary more than tenfold from countries with low incidence, such as Switzerland (25 stroke deaths per 100 000 population aged 40–69 years), to regions with a high stroke risk, such as Eastern Europe, Japan, China, or the Stroke Belt in the south-eastern USA [25]. The meta-analysis of Wolf-Maier *et al.* investigated the hypothesis that average level of BP and its age-related increase might differ across eight countries and might go hand-in-hand with the observed differences in stroke mortality. Average systolic/diastolic BP was 136/83 mmHg in the European countries and 127/77 mmHg in Canada and the USA among men and women combined who were 35–74 years of age. The difference between continents already existed among younger persons (35–39 years) in whom treatment was uncommon (124/78 mmHg versus 115/75 mmHg, respectively).

Interpretation. The increase in systolic blood pressure (SBP) with age was steeper in the European countries. For all age groups, BP values were lowest in the USA and highest in Germany (Fig. 8.6). The age- and sex-adjusted prevalence of hypertension was 28% in the North American countries and 44% in the European countries at the 140/90 mmHg threshold. The findings for men and women by region were similar. Hypertension prevalence was strongly correlated with stroke mortality ($r = 0.78$; Fig. 8.7) and to a lesser degree with total cardiovascular disease ($r = 0.44$).

Comment

As acknowledged by the Wolf-Maier *et al.*, various methodological issues might have biased the findings. Undetected selection in the enrolment of study participants, different lifestyle factors, including salt intake, smoking, or alcohol consumption, divergent secular trends in BP across eight surveys published over a time-span of more than one decade, and climatic influences on BP are among the confounders unaccounted for in her assessment. Furthermore, in all population studies reviewed, with the exception of one survey in England, in which an oscillometric device with doubtful precision [26] had been used, BP was measured by auscultation of the Korotkoff sounds. This technique is prone to error and is difficult to standardize, even among skilled observers. Single or multiple BP readings taken once or even several times during the day, reflect a person's usual BP only to a minor extent. Thus, disparities both in the technique and in the conditions of BP measurement may have inflated the apparent between-country differences in this study.

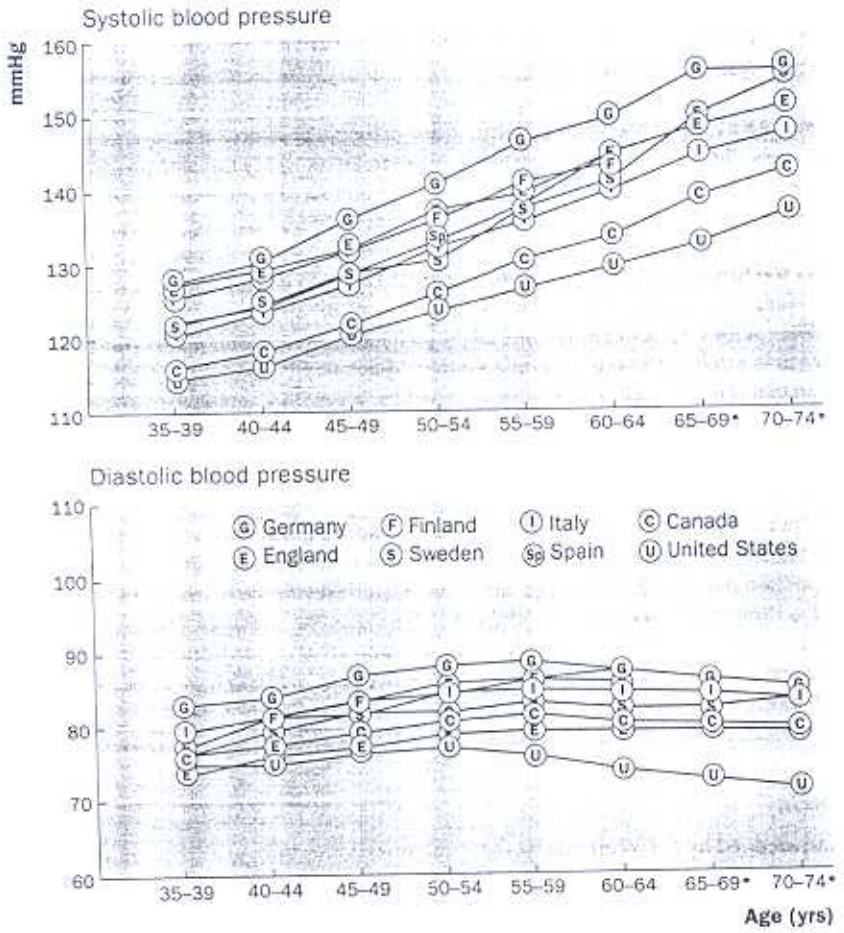

Fig. 8.6 Mean systolic and diastolic blood pressures by age in six European and two North American countries, men and women combined. Asterisks indicate that data for Finland and Spain were not available in the two highest age groups. Source: Wolf-Maier *et al.* (2003).

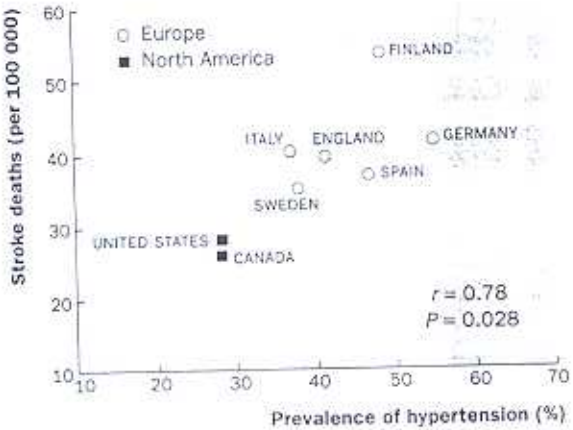

Fig. 8.7 Stroke mortality versus hypertension prevalence in 6 European and 2 North American countries, men and women combined, and age-adjusted. Source: Wolf-Maier *et al.* (2003).

Relationship between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease

Rothwell PM, Howard SC, Spence JD, on behalf of the Carotid Endarterectomy Trialists' Collaboration. *Stroke* 2003; 34(11): 2583–92

Background. For the secondary prevention of stroke, recent guidelines recommend the prescription of BP lowering drugs to normotensive and hypertensive patients with previous cerebrovascular complications. Two large placebo-controlled trials with double-blind designs, namely the Perindopril Protection Against Recurrent Stroke Study (PROGRESS [27]) and the Post-Stroke Antihypertensive Treatment Study (PATS [28]) generated most of the supporting evidence. The BP thresholds delineating hypertension were 160/90 mmHg and 140/90 mmHg, respectively. In a quantitative overview of individual patient data, Rothwell *et al.* studied the relation between stroke risk and BP in patients with a history of transient ischaemic attack or minor stroke, who were randomized in the European Carotid Surgery Trial (ECST [29]), the North American Symptomatic Carotid Endarterectomy Trial (NASCET [30]), or the United Kingdom Transient Ischaemic Attack Aspirin Trial (UK-TIA [31]). Of the ECST and NASCET patients, 64.6% and 38.5% had an ipsilateral carotid stenosis of 50% or more, whereas among the UK-TIA patients this proportion was estimated to be only 6.1%.

Interpretation. In the UK-TIA trial, the risk of recurrent stroke doubled for each 20 mmHg increment in SBP, whereas in the medically treated ECST and NASCET patients,

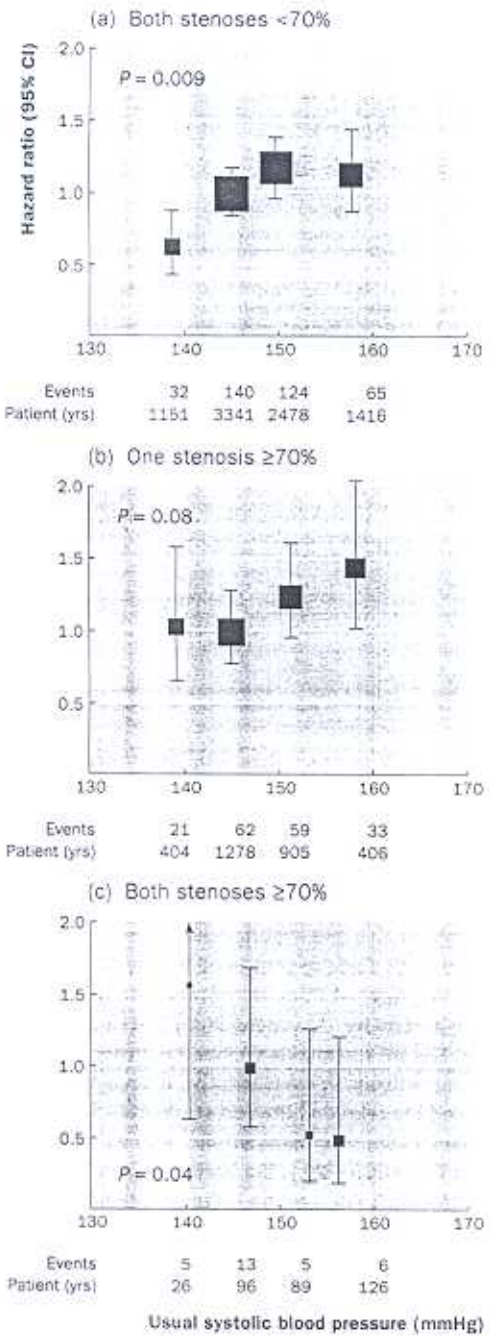

Fig. 8.8 Relation between stroke risk and SBP in patients from NASCET [30] and ECST [29] studies stratified according to severity of carotid disease. The hazard rates were derived from a Cox model stratified by study and adjusted for sex, age, and previous ischaemic heart disease. Source: Rothwell *et al.* (2003).

the corresponding relative risks approximated only 1.5 and were not or just borderline significant. Furthermore, among the ECST and NASCET patients with unilateral carotid lesions, the relation between stroke and BP was positive, whereas among those with bilateral lesions of 70% or more, lower BP was associated with a greater risk of stroke (Fig. 8.8). This interaction between the severity of carotid artery stenosis and BP was specific to stroke, because it was not present after carotid endarterectomy, nor was it observed in relation to myocardial infarction.

Comment

Rothwell *et al.*'s meta-analysis should be interpreted within the context of its limitations. Only 508 UK-TIA patients (20.8%) underwent carotid imaging. At baseline, the UK-TIA [31] population was younger than in the ECST [29] or NASCET [30], had fewer and more recent qualifying strokes, and included less patients with diabetes mellitus. To what extent these differences between the three trials may have impacted on the pooled results is difficult to assess. Nevertheless, the meta-analysis of Rothwell *et al.* highlights that in terms of priority, immediate BP lowering might not be advisable for the group of stroke patients who have bilateral carotid lesions with a lumen narrowing of 70% or more.

About 20% of patients with transient ischaemic attack or stroke have atherosclerosis of the cervical arteries. In the presence of stenotic lesions of the carotid artery, BP falls distal to the stenosis when it narrows the lumen by 70% or more or when the residual lumen diameter drops to 2 mm or less. In the absence of sufficient collateral circulation, low cerebral perfusion pressure can cause ischaemia in the watershed areas between the cerebral vessels. Cerebral ischaemia is more likely to arise when BP proximal of the stenosis is within the normotensive range or when it would be indiscriminately lowered. Moreover, hypertensive patients have a diminished capacity to autoregulate cerebral BP, which increases the vulnerability of the brain in case of a sudden fall in BP or when BP is excessively lowered.

Patients with a history of cerebrovascular disease who have bilateral carotid lesions may first require revascularization before BP lowering therapy is started or intensified. Moreover, in the presence of significant carotid atherosclerosis, risk factor modification including lipid lowering treatment should help to halt or stabilize plaque formation. Antiplatelet therapy with low-dose aspirin or thienopyridines in most patients or antithrombotic therapy in selected patients with atrial fibrillation are also indicated. Whereas progressive BP lowering is key to the secondary prevention of stroke [27,28], this strategy should be part of a more holistic therapeutic approach, which also accounts for anomalies in the cerebral circulation and risk factors other than just BP.

Blood pressure reduction and secondary prevention of stroke and other vascular events—a systematic review

Rashid P, Leonardi-Bee J, Bath P. *Stroke* 2003; **34**(11): 2741–9

BACKGROUND. High BP is a risk factor for stroke recurrence. Rashid *et al.* assessed the effectiveness of BP lowering in preventing recurrent cardiovascular events in patients with a history of cerebrovascular disease. These investigators performed a systematic review and meta-regression of completed randomized controlled trials, which focused on the effects of BP lowering on recurrent vascular events in patients with prior ischaemic or haemorrhagic stroke or transient ischaemic attack. They searched three electronic databases (Cochrane Library, EMBASE, MEDLINE) and reviewed 7 trials including 8 comparison groups.

INTERPRETATION. Lowering BP or treating hypertension with a variety of antihypertensive agents reduced stroke (odds ratio [OR] 0.76, 95% CI 0.63–0.92), non-fatal stroke (OR 0.79, 95% CI 0.65–0.95), myocardial infarction (OR 0.79, 95% CI 0.63–0.92), and total vascular events (OR 0.79, 95% CI 0.66–0.95). Treatment did not affect cardiovascular or all-cause mortality. Rashid *et al.* reported that heterogeneity was present for several outcomes and that it was partly related to the class of antihypertensive drugs used. ACE inhibitors and diuretics given separately, but especially together, reduced cardiovascular events, while β-blockers had no effect. Calcium channel blockers were not used as first-line agents in trials on the secondary prevention of stroke. The reduction of stroke recurrence was related to the difference in SBP between treatment and control groups.

Comment

In line with other quantitative overviews of the literature [32–34], the evidence from the randomized controlled trials reviewed by Rashid *et al.* strongly supports the use of antihypertensive agents in lowering BP for the prevention of recurrent stroke and vascular events in patients with previous stroke or transient ischaemic attack. The level of cardiovascular event prevention increases with the magnitude by which BP is reduced.

Conclusion

To illustrate recent progress along two main lines of epidemiological research, we highlighted the importance of host and environmental factors and lifestyle in the genetic determination of continuous phenotypes (mechanisms of disease), and we reviewed recent publications focusing on the continuous association between cardiovascular complications, in particular stroke and recurrent stroke, and the reversibility of this relation by BP lowering treatment (prevention of disease).

The articles reviewed in the first part of the chapter show the contribution which epidemiology can make to the dissection of complex quantitative traits, such as BP and left ventricular mass, in terms of their polygenic and environmental determination. Until now, the whole genome approach, which is favoured by molecular geneticists, did not yet identify common genetic determinants with major impact on the distribution of BP or left ventricular mass in the population at large [35]. Inbred rat models and genetically engineered mice certainly produced new insights, but rodent models do not stand comparison with the complexity and the heterogeneous nature of human diseases. On the basis of the reviewed articles, we suggest that a more productive approach should involve integration of basic and clinical medicine. Basic scientists will continue to generate the physiological and pathophysiological knowledge to comprehend phenotype–genotype relations, and to generate new *a priori* hypotheses to be tested in humans. Conversely, epidemiological observations unaccounted for by known pathophysiological pathways and confirmed in independent population samples must be further explored in animal experiments and genomic investigation at the molecular level. The four reviewed articles also highlight that ecogenetic context, lifestyle and gene–gene interactions are key to our understanding of the pathogenesis of complex diseases and should be accounted for in future epidemiological research and in the construction of cell and animals models as well.

The articles reviewed in the second part of this chapter along with other systematic overviews [24,32–34] demonstrate that the incidence of cardiovascular complications is positively and continuously related to BP [24]. Small gradients in BP between the groups randomized in recently published primary and secondary prevention trials explain most of the observed differences in cardiovascular outcomes [32–34]. The combined evidence from placebo-controlled and actively controlled trials [33,34] demonstrates that, in general, thiazide diuretics and long-acting dihydropyridine calcium channel blockers are most effective in preventing the cerebrovascular complications of hypertension. Compared with diuretics [27,28,36] therapy initiated with ACE inhibitors is less effective, especially in older [36] and non-Caucasian [27,28,36] patients.

However, the answer as to which drug class is better suited to start antihypertensive therapy is largely elusive. In most patients, optimization of treatment at acceptable tolerance requires rotation through and combination of several drug classes [37]. The BP lowering activities of ACE inhibitors and β-blockers are additive to those of thiazides and calcium channel blockers and vice versa [37]. As illustrated by Wolf-Maier's group [38], doctors, health care providers and policy makers should join efforts to increase the control rate of patients with hypertension to far above the current average of approximately 25% of those in the community and 50% of those actually diagnosed.

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9

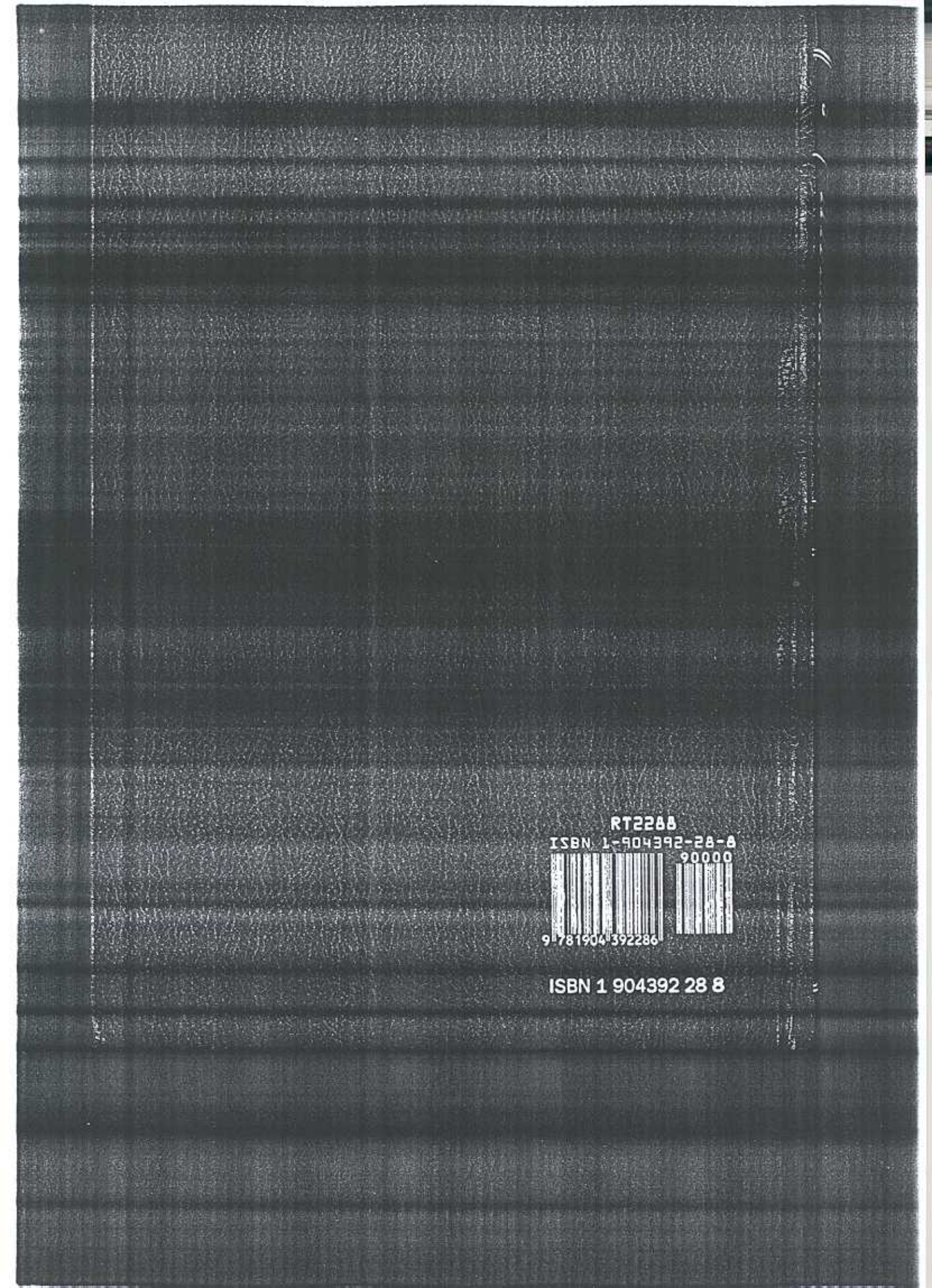
Clinical trials of antihypertensive drugs

HANS BRUNNER, IRENE GAVRAS

Introduction

Modern treatment of hypertension is one of the great success stories of medicine. Nevertheless, it is under-appreciated because the topic does not have the eye-catching appeal and newsworthiness of a daring application of new technology to correct a medical disaster, or reversal of an aberration of nature. It is difficult to estimate the number of patients' events that failed to occur as a result of antihypertensive therapy, but preventing hypertensive complications has quietly preserved or improved the health and prolonged the life of millions of beneficiaries.

The first effective antihypertensives were introduced in the 1950s, and the first randomized placebo-controlled trials were conducted in the 1960s. The landmark Veterans Administration trials [**1,2**] proved beyond doubt that lowering blood pressure (BP) with the agents then available – diuretics and sympatholytics – could significantly decrease the rate of stroke, kidney failure and progression to accelerated/malignant hypertension, although the incidence of coronary disease did not seem to be significantly affected. Thiazide diuretics, along with the β-adrenergic blockers, which were introduced in the 1970s, became the staple antihypertensives and were shown to greatly enhance BP control. The angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) were introduced in the 1980s and the angiotensin II AT_1 receptor blockers (ARBs) in the 1990s. New agents were compared against a thiazide or β-blocker, and if they were comparable to the 'gold standard' in terms of antihypertensive efficacy and tolerability, the Federal Drug Administration (USA) and medical community at large accepted them. As long as the benefit of antihypertensive treatment could be solely attributed to the degree of BP lowering, any effective drug was considered to be equivalent to any other, with cost, availability and convenience being the distinguishing factors. The Joint National Committee (JNC) VI and VII guidelines [**3,4**] recommended that antihypertensive therapy should start with a thiazide or β-blocker as first choice and the newer, still patented, drugs should be added in special circumstances only. Nevertheless, a number of clinical scientists felt, on the grounds of basic, experimental and clinical research, that drugs inhibiting the renin–angiotensin system (RAS) should be at least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